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EXAMINER

SULLIVAN, DANIEL M

ART UNIT PAPER NUMBER

1636

DATE MAILED: 05/03/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/644,080

Applicant(s)

UNGER ET AL.

Examiner

Daniel M. Sullivan

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 9 Feb 2005, 27 Oct 2005, 8 Feb 2006.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 105-120 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 105-120 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|--|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input checked="" type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

This Office Action is a reply to the Papers filed 9 February 2005, 27 October 2005 and 8 February 2006 in response to the Non-Final Office Action mailed 24 August 2004. Claim 1 was considered in the 24 August Office Action. Claim 1 was canceled and claims 105-120 were added in the 9 February Paper. Claims 105-120 are pending.

Election/Restrictions

Applicant's election with traverse of the synthetic dipeptide N-acetyl-muramyl-L-alanyl-D-isoglutamine as the compound to be delivered and 2-chloro-1,1,1,4,4,4-hexachloro-2-butene as the species of organic halide in the 27 October Paper is acknowledged. The traversal is on the ground(s) that the number of members of the Markush group is sufficiently few so that a search and examination can be made without a serious burden on the examiner. This is not found persuasive because the claims recite nearly 90 distinct species of organic halide and nearly 300 species of compound or class of compound to be delivered, which would result in many thousands of possible combinations of compound and organic halide in claim 116. Clearly, searching all of the embodiments recited in the claims would constitute a serious burden on the Office.

The requirement is still deemed proper and is therefore made FINAL.

Claims 106 and 107 withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the 27 October reply

Response to Amendment and Arguments

Rejection of claim 1 is rendered moot in view of the cancellation thereof.

Claim Objections

Claim 117 is objected to because of the following informalities: The claim contains a typographical error in line 1 (*i.e.*, “The method of claim 1161”). Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 119 and 120 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

The MPEP states, “[i]f new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. §112, first paragraph-written description requirement. *In re Rasmussen*, 650 F.2d 1212, 211 USPQ 323 (CCPA 1981).” (MPEP § 2163.06). The MPEP further states,

“[w]henever the issue arises, the fundamental factual inquire is whether a claim defines an invention that is clearly conveyed to those skilled in the art at the time the application was filed...If a claim is amended to include subject matter, limitations, or terminology not present in the application as filed, involving a departure from, addition to, or deletion from the disclosure of the application as filed, the examiner should conclude that the claimed subject matter is not described in the application” (*Id.*, § 2163.02). The introduction of claim changes which involve narrowing the claims by introducing elements or limitations which are not supported by the as-filed disclosure is a violation of the written description requirement of 35 U.S.C. 112, first paragraph. See, e.g., *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1571, 39 USPQ2d 1895, 1905 (Fed. Cir. 1996).

The claims are directed to a method for delivering a compound into a cell *in vitro* or *in vivo* comprising applying ultrasound to said cell at 200-500 milliwatts per cm^2 . The application as filed does not define a range specifically delimited by 200 and 500 milliwatts per cm^2 . Instead, the specification teaches, “Preferably, the ultrasound is in the frequency range of from about 10 kilohertz to less than about 50 megahertz and at an energy level of from about 200 milliwatts/ cm^2 to about 10 watts/ cm^2 ” (§ bridging p. 47-48) and “Typically, the energy level settings are somewhat higher than employed in diagnostic ultrasound but may range from about 500 milliwatts/ cm^2 to about 10 watts/ cm^2 , more preferably from about 200 milliwatts/ cm^2 to about 10 milliwatts/ cm^2 , and more preferably of from about 50 milliwatts/ cm^2 to about 2 watts/ cm^2 ” (p. 49, ¶2). These teachings contain neither explicit nor implicit support for the range presently recited in the claims. In particular, as 500 milliwatts/ cm^2 is only recited as a lower limit of the range 500 milliwatts/ cm^2 to about 10 watts/ cm^2 none of the teachings found in the

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specification would suggest 500 milliwatts/cm² as an upper limit for a range of energy to be used in the method. Thus, the method of claims 19 and 20 wherein the application of ultrasound is limited to the range of 200-500 milliwatts/cm² constitutes impermissible new matter.

Claims 105 and 108-120 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for delivering a nucleic acid into a cell comprising administering a composition comprising a nucleic acid and an organic halide, wherein the composition further comprises a lipid carrier or wherein ultrasound is applied to said cell, does not reasonably provide enablement for the broad scope of a method of delivering any compound into a cell by administration of said compound with any organic halide. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

This rejection was set forth against claim 1 in the 24 August Office Action. The rejection is substantially reiterated herein below with modification and additional references provided necessitated by the additional limitation of the new claims to the absence of a liposome and the applying of ultrasound sufficient to induce uptake of the compound into the cell.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (a) the nature of the invention; (b) the breadth of the claims; (c) the state of the prior art; (d) the amount of direction provided by the inventor; (e) the existence of working examples; (f) the relative skill of those in the art; (g) whether the quantity of experimentation needed to

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make or use the invention based on the content of the disclosure is "undue"; and (h) the level of predictability in the art (MPEP 2164.01 (a)).

Nature of the invention and Breadth of the claims: The claim broadly encompasses a method wherein a compound is introduced into a cell by administering said compound in a composition that further comprises an organic halide. The claims additionally recite that ultrasound is applied sufficient to induce uptake of the compound into the cell and the mixture administered does not comprise a liposome (claims 105 and 108-118). Organic halide is defined in the fourth full paragraph on page 6 of the specification as a compound containing at least one carbon atom (or optionally sulfur or selenium atom) and at least one halogen atom selected from the group consisting of fluorine, chlorine, bromine or iodine. Thus, the organic halide of the claims broadly encompasses a very large genus of structurally and functionally divergent molecules. In the first full paragraph on page 15, the specification teaches, "[a] wide variety of compounds can comprise the compounds to be delivered to the cells in accordance with the invention, including bioactive agents, diagnostic agents, pharmaceutical agents, and the like, and include proteins, DNA and RNA..." Thus, the compound of the claims is of essentially unlimited scope. Furthermore, on page 14, the specification teaches, "[i]ntracellular delivery includes delivery into the cells through a cell membrane (plasma membrane), cell wall, and/or nuclear membrane" (second full paragraph).

Viewed as a whole, the claims encompasses a method of extraordinary breadth, wherein essentially any compound is delivered through a cell membrane, cell wall and/or nuclear membrane in combination with a compound containing at least one carbon atom (or optionally sulfur or selenium atom) and at least one halogen atom selected from the group consisting of

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fluorine, chlorine, bromine or iodine. Although, the Office has acknowledged that the method is enabling for delivering a nucleic acid into a cell comprising administering a composition comprising a nucleic acid and an organic halide, wherein the composition further comprises a lipid carrier or wherein ultrasound is applied to said cell (U.S. Patent Nos. 6,638,767 and 6,743,779), the specification fails to enable the method beyond this scope.

State of the prior art and level of predictability in the art: With regard to the broad scope of delivering compounds other than nucleic acids into cells, the art teaches delivery of many compounds across cell walls and membranes has proved more difficult than for the structurally homogeneous nucleic acid molecule. For example, in spite of tremendous interest in delivering peptides and proteins into cells, there have been very few molecules identified as capable of providing non-invasive delivery of peptides and proteins. Hawinger (1999) *Curr. Opin. Chem. Biol.* 3:89-94 teaches, “[t]he plasma membrane of eukaryotic cells is inherently impermeable to peptides and proteins that lack specialized membrane receptors or transport proteins” (paragraph bridging pages 89-90) and “invasive techniques of microinjection or applications of membrane-disrupting pore-forming reagents...are usually employed to introduce antibodies, synthetic peptides or other noncell membrane-permeable molecules into cells” (sentence bridging the left and right columns on page 89). Although Hawinger goes on to teach that a very limited number of peptide molecules have been identified as capable of facilitating intracellular delivery of some peptides and proteins (see especially Table 1), Veach *et al.* (2004) *J. Biol. Chem.* 279: 11425-11431 teaches that as of 2004 the mechanism by which these peptides translocate cargo across the plasma membrane remained unexplained (paragraph bridging the left and right columns on page 11425). Thus, the combined teachings of Hawinger and Veach *et al.* show that, even many

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years after the effective filing date of the instant application, development of methods to introduce a very large class of compounds (*i.e.*, peptides and proteins) into a cell was at a very early stage of development. Therefore, the skilled artisan would not be able to readily practice the method as it encompasses delivery of peptides, proteins or other non-nucleic acid molecules into cells without specific guidance as to which organic halide compounds would be capable of providing transport across the membrane.

Although the claims are now limited to the application of ultrasound to the mixture sufficient to induce uptake of the compound into a cell, it is noted that the claims generically embrace delivery of any molecule into any cell using any composition that comprises an organic halide. Furthermore, as discussed above, the specification teaches, intracellular delivery includes delivery into the cells through a cell wall (*i.e.*, delivery into plant and bacterial cells). The art provides several teaches indicating that successfully delivering any given molecule into any given cell by a method comprising administering the agent and any organic halide and applying ultrasound would be unpredictable. First, with respect to successfully delivering a compound across a cell wall by a method comprising applying ultrasound, the art is silent. With regard to delivering compounds into cells that do not comprise a cell wall, the art teaches that successfully practicing the claimed method wherein the composition comprises any given compound and any given organic halide is unpredictable. Van Wamel *et al.* (2006) *J. Controlled Rel.* (published online at www.sciencedirect.com) teaches, "The degree of membrane permeabilization, molecular uptake and cell survival upon membrane poration depends critically on the frequency and duration of the applied [ultrasound] field pulses[.]. Although much progress is made elucidating the ultrasound parameter effects, the fundamental physical processes behind the

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[ultrasound contrast agent] induced membrane alterations are not well understood. In today's research, the used conditions of ultrasound microbubble enhanced drug uptake are trial and error based and therefore probably far from optimal." (§ bridging pp. 1-2; citations omitted). Likewise, although Guzman *et al.* (2003) *Ultrasound in Med. & Biol.* 8:1211-1222 teaches that there are some examples of using ultrasound to deliver protein and DNA in to tissue, Guzman *et al.* also teaches, "These bioeffects are believed to be caused by oscillations and/or implosion of ultrasonically generated cavitation bubbles that reversibly break open cell membranes []. When not properly controlled, cavitating bubbles can also cause irreversible cell damage, resulting in significant cell death []. For this reason, controlled amounts of contrast agent, CA, microbubbles have been added during sonication to serve as cavitation nuclei" (p. 1211, col. 2, ¶1). Pitt *et al.* (2006) *Expert Opin. Drug Deliv.* Teaches, "**1.3.2.3 Cell permeabilization and capillary rupture** The third major contribution of ultrasound to drug delivery relates to stresses inflicted upon cells and tissues and a result of cavitation events. Ultrasound by itself, in the absence of cavitation, is thought to have little if any effect on cells and tissues apart from some heating that may occur at higher frequencies and intensities []. As with vesicles, cells in an environment of cavitation events are subjected to shear from microstreaming, shock waves and sonic jets" (p. 4; citations omitted). Viewed as a whole, the art teaches that delivery of agents into cells is critically dependent upon cavitation events which must be controlled in order to obtain membrane permeabilization without cell rupture. Although the post filing art teaches that the addition of microbubbles provides for some control of these cavitation processes, the instant claims broadly encompass delivery in the absence of any contrast agent to facilitate controlled permeabilization of membranes.

Amount of direction provided by the inventor and existence of working examples: The working examples disclosed in the instant application demonstrate enhanced delivery of nucleic acids into HeLa cells by treatment with ultrasound (Tables 5 and 6) into various cell lines by addition of perfluorohexane, bromononafluorobutane, perfluoropentane, perfluorooctane and perfluorodecane (Tables 7-13). However, the disclosure provides no working examples of the claimed method wherein any molecule other than a nucleic acid is delivered across a plasma membrane or wherein any molecule at all is delivered across a cell wall using ultrasound.

Although the specification need not contain an example if the invention is otherwise disclosed in such manner that one skilled in the art will be able to practice it without an undue amount of experimentation, *In re Borkowski*, 422 F.2d 904, 908, 164 USPQ 642, 645 (CCPA 1970), lack of a working example is a factor to be considered, especially in a case involving an unpredictable and undeveloped art. The art cited above clearly establishes that the ability to facilitate delivery of compounds such as nucleic acids and proteins across the plasma membrane of a cell is a characteristic of only a few compounds. Further, the art teaches that the structural characteristics that confer the ability to transport other molecules across the plasma membrane were not established such that, at the time of filing, the skilled artisan could readily identify an organic halide capable of delivering a compound across a plasma membrane. Thus, the relevant art is clearly established to be undeveloped and unpredictable. Although the specification suggests various preferred embodiments of the claimed invention (*e.g.*, Table 1), no evidence is provided to indicate that any of these embodiments would have the capacity to deliver any compound across the plasma membrane of a cell in the absence of a lipid carrier or ultrasound

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and no evidence is provided to indicate that any compound other than a nucleic acid could be delivered into a cell according to the claimed method.

By way of theory, the specification provides, "it is believed that delivery of nucleic acid sequences and other compounds in accordance with the methods of the present invention may induce a cell to take up the compound to be delivered thereto. Included within the definition of delivery of a compound into a cell in accordance with the methods of the present invention are active and passive mechanisms of cellular uptake. Ion channels and other means of transport utilized by cells to incorporate extracellular materials, including compounds to be delivered thereto, into the intracellular milieu are encompassed by the present invention" (page 13).

However, given the teachings from the art, which suggest that only a small fraction, if any, of the organic halides of the claims would be capable of facilitating transport of a compound across the plasma membrane one of ordinary skill in the art would not know which organic halide could be used to deliver any given compound into a cell.

Relative skill of those in the art and quantity of experimentation needed to make or use the invention: Although the relative level of skill in the art is high, one of ordinary skill would not be able to practice the full scope of the claimed invention without engaging in undue experimentation. Given the expansive scope of the claimed subject matter, wherein essentially any organic halide is used to deliver essentially any compound into a cell in the presence of applied ultrasound, and the teachings from the art which indicate that the ability of deliver a compound across the plasma membrane is an unpredictable property of a small set of compounds, the skilled artisan would expect that the claimed method encompasses a tremendous number of inoperative embodiments. Furthermore, the application does not contain a single

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example of delivery of a compound other than a nucleic acid into a cell in the presence of ultrasound. Given that delivery of molecules other than nucleic acids into cells by application of ultrasound was at an early stage of development as of the effective filing date of the application, as evidenced by the absence of a single working example of record as of the effective filing date of the instant claims, and teachings in the post filing art that parameters such as the inclusion of compounds to control cavitation events are critical to effective delivery, developing the claimed method using ultrasound to deliver any molecule into any cell would require undue experimentation.

The skilled artisan seeking to practice the instant claimed method according to its full scope would be forced to identify which of the many thousands of combinations of organic halide and compound encompassed by the claims would be operative in a method of introducing a compound into a cell and determine how to apply ultrasound sufficient to induce uptake of any compound into any cell. By way of guidance in determining the operative embodiments of the invention, the specification provides only suggestions of preferred embodiments of the organic halide and very limited working examples, which provide the method practiced with a single compound (*i.e.*, DNA) and five species of organic halide, wherein the composition further comprises additional ingredients (*i.e.*, transfection reagents) that would provide delivery of a nucleic acid into a cell even in the absence of the organic halide. Given these teachings the skilled artisan would have no idea which embodiments of the claimed invention would be operative, beyond those wherein the compound is a nucleic acid and the method further comprises a lipid carrier or application of ultrasound. Thus, operability of each of the many thousands of combinations encompassed by the claims would have to be determined

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independently by empirical experimentation. Clearly, therefore, determining which embodiments of the claimed invention that were conceived, but not yet made, would be inoperative or operative would require tremendous effort and places an undue burden on one of ordinary skill seeking to practice the invention. Therefore, the claim is rejected under 35 U.S.C. §112, first paragraph, as lacking enablement for the full scope of the claimed subject matter.

Response to Arguments

In response to the rejection set forth against claim 1, Applicant contends that the teachings of Godbey *et al.* do not suggest that use of organic halides to deliver compounds into cells would be unpredictable because Godbey does not specifically discuss the use of organic halides as delivery agents.

This argument is not deemed persuasive because Godbey *et al.* generally teaches that the structural elements that define an effective delivery agent are unpredictable. While it is true that Godbey *et al.* does not specifically address organic halides, there is nothing of record that would indicate that organic halides are not subject to the same unpredictability as the molecules specifically addressed by Godbey *et al.* In fact, as the molecules considered by Godbey are organic, the only difference between those molecules and the organic halides of the claims is that the organic halides comprise at least one halogen atom. Clearly, there is no reason to believe that the teachings of Godbey are irrelevant to organic halides because organic halides comprise a halogen atom and the teachings of Godbey are based on molecules that comprise everything except for a halogen atom.

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With regard to the teachings of Hawiger *et al.* and Veach *et al.*, Applicant again contends that the art does not apply to the instant claims because the art is not specifically directed to the use of organic halides. While it is true that the teachings of Hawiger *et al.* and Veach *et al.* are not specifically directed to delivery using organic halides, the teachings are clearly relevant insofar as they demonstrate that the art recognizes delivering a protein across a cells plasma membrane by any means as unpredictable. It is noted that a showing that the field of endeavor (delivery of molecules across the plasma membrane in the instant case) is relevant to considering whether the claims are enabled. MPEP 2164.04 states:

The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling. See, e.g., *Chiron Corp. v. Genentech Inc.*, 363 F.3d 1247, 1254, 70 USPQ2d 1321, 1326 (Fed. Cir. 2004) (“Nascent technology, however, must be enabled with a specific and useful teaching.” The law requires an enabling disclosure for nascent technology because a person of ordinary skill in the art has little or no knowledge independent from the patentee’s instruction. Thus, the public’s end of the bargain struck by the patent system is a full enabling disclosure of the claimed technology.” (citations omitted)).

The “predictability or lack thereof” in the art refers to the ability of one skilled in the art to extrapolate the disclosed or known results to the claimed invention. If one skilled in the art can readily anticipate the effect of a change within the subject matter to which the claimed invention pertains, then there is predictability in the art. On the other hand, if one skilled in the art cannot readily anticipate the effect of a change within the subject matter to which that claimed invention pertains, then there is lack of predictability in the art. Accordingly, what is known in the art provides evidence as to the question of predictability.

With regard to the disclosure by Hawiger *et al.* and Veach *et al.* of translocating polypeptides capable of transporting cargo across the plasma membrane, the existence of those molecules does not support enablement for the instant claims, as implied in Applicant’s remarks, because their existence does not suggest that one can readily anticipate the effect of a change

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within the subject matter to which the claimed pertains. In other words, the examples of some operative embodiments within a generally unpredictable art does not support broad enablement for a method of delivering any compound into any cell using any organic halide.

With regard to the contention in the previous Office Action that there is no evidence to indicate that any compound other than a nucleic acid could be delivered into a cell by the claimed method, Applicant points to the teaching at pages 42-45 of the specification. However, the cited teaching is merely a laundry list of compounds, which the application prophetically states can be delivered into cells. The teaching is not evidence that compounds other than nucleic acids can be delivered by the method claimed.

Next, Applicant contends that the teachings of Godbey, Hawiger and Veach rather than suggesting the unpredictability of delivering compounds into, actually demonstrate that delivery has been accomplished. Applicant contends none of the references suggest that only a small fraction of organic halides is capable of facilitating transport of a protein across a plasma membrane.

This argument is not deemed persuasive. As discussed herein above, the question of unpredictability concerns whether the skilled artisan can readily anticipate the effect of a change within the subject matter to which that claimed invention pertains. In view of the teachings found in the cited art, which indicate that the structural characteristics required to provide delivery of a compound into a cell are unknown, the skilled artisan clearly could not readily anticipate the effect of a change within a given organic halide. The teachings of Godbey, Hawiger and Veach clearly suggest that the capacity to deliver molecules across the plasma membrane of cells is a property of only a very few molecules and, as discussed above, the only difference between

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those molecules considered by Godbey and the organic halides of the claims is that the organic halides comprise at least one halogen atom. As stated above, there is no reason to believe that the teachings of Godbey are irrelevant to organic halides because organic halides comprise a halogen atom and the teachings of Godbey are based on molecules that comprise everything except for a halogen atom.

Applicant further contends that the cited art does not apply because the newly filed claims do not recite transporting compounds in the absence of ultrasound. This argument is not deemed persuasive in view of the additional art cited herein above to evidence the unpredictable nature of delivering compounds into cells using ultrasound. The art provides several teachings indicating that successfully delivering any given molecule into any given cell by a method comprising administering the agent and any organic halide and applying ultrasound would be unpredictable. Absent evidence to the contrary, the nature of the organic halide used in the method is considered critical to providing an effective outcome in the method and, therefore, the teachings of the art demonstrating the unpredictable nature of agents capable of enabling transport of agents across the cell membrane are still relevant to what is presently claimed.

Finally, Applicant contends that there is no evidence that any of the embodiments within the scope of what is claimed would be inoperative. Applicant contends that without a showing that any of the embodiments might be inoperative, the Office Action has failed to establish any of the embodiments disclosed in the specification.

This argument has been fully considered but is not deemed persuasive. Applicant is reminded that the organic halide of the claims is defined in the fourth full paragraph on page 6 of the specification as a compound containing at least one carbon atom (or optionally sulfur or

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selenium atom) and at least one halogen atom selected from the group consisting of fluorine, chlorine, bromine or iodine and the method is directed to delivering any compound into any cell. Thus, the organic halide of the claims embraces a vast genus of molecules, while the art cited in the Office Action teaches that very few molecules have been demonstrated to have the capability of delivering molecules into cells. For example, as pointed out in the previous Office Action (page 8) Hawiger teaches, “[t]he plasma membrane of eukaryotic cells is inherently impermeable to peptides or proteins”. Peptides and proteins are, of course, organic molecules. As there is no reason to believe that the presence of a halogen atom in a peptide, protein or even an amino acid would suddenly render it capable of delivering any compound into any cell, it is reasonable to conclude that the vast majority of halogenated peptides, proteins and amino acids would be inoperative in the method. Therefore, it is also reasonable to conclude that there is a large genus of inoperative embodiments within the scope of what is presently claimed.

Applicant’s arguments have been fully considered but are not deemed persuasive in view of the record as a whole. Therefore, the claims are properly rejected under 35 USC §112, first paragraph, as lacking enablement for the claimed subject matter.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

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The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 19 and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Unger (WO 94/28780; made of record in the previous Office Action).

Unger *et al.* teaches a method of expressing an exogenous nucleic acid sequence in a cell comprising the steps of: delivering said nucleic acid sequence to together with a halide compound into the cell. In the Examples beginning on page 70 and continued through page 87, Unger *et al.* teaches a method of making gaseous precursor-filled liposome microsphere or microbubble and the administration of said microspheres with a variety of perfluorocarbons (see especially Table II). Unger *et al.* further teaches that these microspheres can be used to deliver genetic material-including RNA, DNA and antisense RNA-for expression in heterologous cells

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(see especially beginning the second full paragraph of page 64 and continued through the first paragraph on page 65). Furthermore, Unger *et al.* teaches that the method of using the microspheres can comprise the application of sonic energy (see, *e.g.*, p. 52, ¶1 and p. 57, ¶2). In the discussion on page 57 and 58, Unger *et al.* contemplates various parameters for the application of ultrasound. Although, Unger *et al.* fails to teach that energy should be applied at 200-500 milliwatts per cm^2 , this limitation does not distinguish the claimed method from the method of Unger *et al.*

The instant application teaches that ultrasound in the range from about 500 milliwatts/ cm^2 to about 10 watts/ cm^2 , more preferably from about 200 milliwatts/ cm^2 to about 10 milliwatts/ cm^2 , and more preferably of from about 50 milliwatts/ cm^2 to about 2 watts/ cm^2 is typical of therapeutic ultrasound (p. 49, ¶2). Unger *et al.* teaches, “Higher energy ultrasound such as commonly employed in therapeutic ultrasound equipment is preferred for activation of the therapeutic containing gaseous precursor-filled liposomes” (p. 56, ll. 16-19). Thus, the only distinction between what is claimed and what is taught in the prior art is the recitation in the claim of what appears to be an optimum range, which difference does not support patentability of subject matter claimed. “[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.” *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955) (Claimed process which was performed at a temperature between 40°C and 80°C and an acid concentration between 25% and 70% was held to be prima facie obvious over a reference process which differed from the claims only in that the reference process was performed at a temperature of 100°C and an acid concentration of 10%.); see also *Peterson*, 315 F.3d at 1330, 65 USPQ2d at 1382 (“The normal

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desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages.”); *In re Hoeschele*, 406 F.2d 1403, 160 USPQ 809 (CCPA 1969) (Claimed elastomeric polyurethanes which fell within the broad scope of the references were held to be unpatentable thereover because, among other reasons, there was no evidence of the criticality of the claimed ranges of molecular weight or molar proportions.). For more recent cases applying this principle, see *Merck & Co. Inc. v. Biocraft Laboratories Inc.*, 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989); *In re Kulling*, 897 F.2d 1147, 14 USPQ2d 1056 (Fed. Cir. 1990); and *In re Geisler*, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997).

In view of the foregoing, the invention of claims 119 and 120, as a whole, would have been obvious to one of ordinary skill in the art at the time the invention was made based on the teachings of Unger *et al.* Therefore, the claims are properly rejected under 35 USC §103(a) as obvious over the art.

Closest Prior Art

Reinhardt *et al.* US Patent No. 5,425,366 teaches the production of microparticles consisting of a synthetic biodegradable polymer and a gas (see especially col. 5, ll. 31-50), wherein the preferred gasses include various organic halides (see col. 5, ll. 59-68). Reinhardt *et al.* further teaches a method wherein the microparticles are delivered into a patient and administration of ultrasound at an energy level sufficient to induce bursting of the microparticles (see especially col. 3, l. 43 through col. 5, l. 13). Thus, the method of Reinhardt *et al.* comprises

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administering a microparticle composition comprising a compound (*i.e.*, a synthetic biodegradable polymer) and an organic halide, wherein the composition does not comprise a liposome, and applying ultrasound at an energy level sufficient to burst the microparticle. The art has not been applied to the instant claims because, for the reasons stated in the previous Office Action and herein above, it is not considered to be enabling for a method for delivering a compound into a cell. However, if one were to accept applicant's arguments with regard to broad enablement for what is presently claimed one would also conclude that, because the method of Reinhardt *et al.* comprises all of the elements of the claimed method delivery of a compound into a cell would be inherent to the method of Reinhardt *et al.* Therefore, in the event that Applicant is able to establish that the instant claims are generally enabled, Reinhardt *et al.* will be applied under 35 USC §102(a) and/or (e) unless Applicant can establish a patentable distinction or that the teachings of Reinhardt *et al.* are not enabling for a method of delivering a compound into a cell.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period

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will expire on the date the advisory action is mailed, and any extension fee pursuant to 37

CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel M Sullivan whose telephone number is 571-272-0779. The examiner can normally be reached on Monday through Friday 6:30-3:00.


If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

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